DETAILED ACTION

This office action is in response to applicant's reply filed on June 21, 2011.

Receipt of Declarations under 37 CFR 1.132 is acknowledged.

Status of Claims

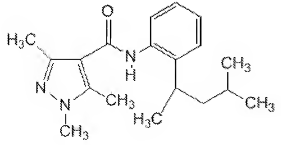
Amendment of claims 11-12 is acknowledged

Claims 11-14, and 17-18 are currently pending and are the subject of this office action.

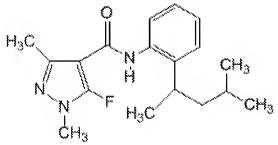
Claim 18 was withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on July 14, 2008.

Claims 13-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species (see discussion below), there being no allowable generic or linking claim.

Applicant elected the following species in the reply filed on 07/14/08:

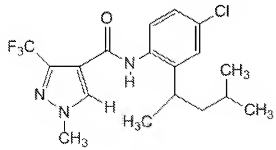


In the Office Action mailed on 10/29/08, the elected species was found free of prior art, so the examination was expanded to the following species: N-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1H-pyrazole-4-carboxamide (CAS# 494793-67-8):

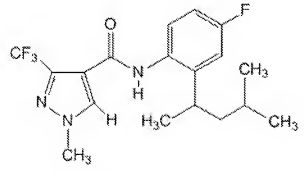


The same species was used in the Office Action mailed on 04/24/09.

Due to Applicant's amendment of the claims in the reply filed on 07/31/09, the above species no longer read on the instant claims. So the examination was expanded to the following species: N-[4-Chloro-2-(1,3-dimethylbutyl)phenyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (CAS# 203448-85-5):

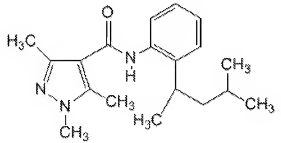


Due to Applicant's amendment of the claims in the reply filed on 01/26/10, the above species no longer read on the instant claims. So the examination was expanded to the following species:

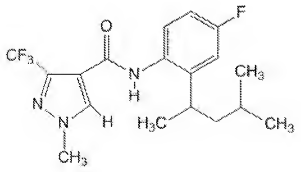


from now on Compound A.

In summary, the following species are under examination:



elected by Applicant on 07/14/08, which is free of prior art, and



(Compound A).

The following claims read on one or both species and are under examination: 11-12 and 17. As such Claims 13-14 are further withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention/species, there being no allowable generic or linking claim.

NOTE: the above clarifies Applicant's concerns (see pages 8 and 9 of Applicant's remarks dated 06/21/11) regarding restriction requirements and species being examined.

Priority

The present application is a 371 of PCT/EP04/11394 filed on 10/12/2004, and claims priority to foreign application GERMANY 10349502.9 filed on 10/23/2003.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103(Maintained Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

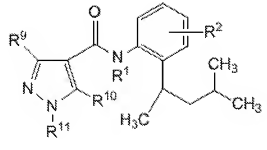
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

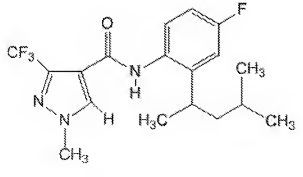
consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-12 and 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshikawa (US 5,914,344, cited in previous office action) in view of Patani et. al. (Chem. Rev. (1996) 96:3147-3176, cited in prior office action).

Claims 11 and 12 recite a compound of general formula I:



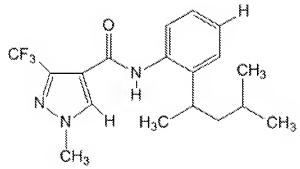
which encompasses the following compound:



(Compound A, see also example 12 on page 41 of the specification).

For claims 11 and 12, Yoshikawa teaches the following compound:

N-[2-(1,3-dimethylbutyl)phenyl]-1-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (CAS# 203448-69-5):



(See column 17, lines 40-45, Example 2, from now on Compound B), which differs from compound A, in that the aromatic ring is substituted with Hydrogen instead of Fluorine.

Patani teaches that the substitution of Hydrogen by Fluorine is one of the most commonly employed monovalent isosteric replacements (see page 3149, left column under 1. Fluorine vs. Hydrogen Replacements). Further, in Figure 2 on the same page they give an example wherein replacing Hydrogen with Fluorine in an aromatic ring maintains or improves the pharmacological properties of the compounds. In summary, substituting Hydrogen by Fluorine is routine practice in the pharmaceutical art, and should not drastically alter the biological/pharmaceutical properties.

Further, MPEP 2144.09, Section III states: prior art structures do not have to be true homologs or isomers to render structurally similar compounds *prima facie* obvious. *In re Payne*, 606 F.2d 303, 203 USPQ 245 (CCPA 1979) (Claimed and prior art compounds were both directed to heterocyclic carbamoyloximino compounds having

pesticidal activity. The only structural difference between the claimed and prior art was that the ring structures of the claimed compounds had two carbon atoms between two sulfur atoms, whereas the prior art ring structures had either one or three carbon atoms between two sulfur atoms. The court held that although the prior art compounds were not true homologs or isomers of the claimed compounds, the similarity between the chemical structures and properties is sufficiently close that one of ordinary skill in the art would have been motivated to make the claimed compounds in searching for new pesticides). In *re Gyurik*, 201 USPQ 552, 596 F2d 1012 on page 557 states: "In obviousness rejections based on close similarity in chemical structure, the necessary motivation to make a claimed compound, and thus the *prima facie* case of obviousness, rises from the expectation that compounds similar in structure will have similar properties." In this case it is expected, as discussed above, that compounds differing only by the presence or absence of Fluorine in the aromatic ring, would have similar chemical, physical and biochemical properties as discussed above.

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to replace any aromatic Hydrogen Compound B with a Fluorine in order to obtain compound A, and expect these compounds to have the same biological/pharmaceutical properties, since the prior art teaches replacing Hydrogen with Fluorine is routine practice in the pharmaceutical art (see Patani above) and will not alter significantly the chemical and biological properties of these molecules, thus resulting in the practice of claims 11-12 with a reasonable expectation of success.

Claim 17 further limits claim 11, wherein the compound of formula I is in a composition comprising one or more extenders and/or surfactants.

For claim 17, Yoshikawa further teaches that the compounds of the invention are plant disease control agents (see column 1, lines 8-13) which can be used in formulations that comprise adjuvants (i.e. surfactants) like the ones listed in column 16, lines 13-28 and other nonionic surface active agents.

Response to 37 CFR 1.132 declaration.

The declaration under 37 CFR 1.132 filed on June 21, 2011 is insufficient to overcome the rejection of claims 11-12 and 17 based upon 35 U.S.C. 103 (a) as set forth in the last Office action.

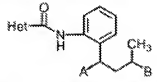
For a full response to the arguments presented by Peter Dahem and Ulrike Wachendorff-Neumann, please see discussion below.

Response to Applicant's arguments related to the above rejection

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues that:

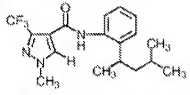
> Claims 11-12 and 17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,914,344 ("Yoshikawa et al") in view of Patani et al, *Chem. Rev.*, 96, 3147-3176 (1996) ("Patani et al article"). Applicants respectfully traverse.
>
> As fully discussed in Applicants Amendment dated January 26, 2010, Yoshikawa et al discloses carboxanilide derivatives of the formula



(where the formula is drawn in the same orientation as shown in Applicants' claims for clarity) in which **Het** can be one of the heterocyclic groups 

(il1) (where R^1

is trifluoromethyl or difluoromethyl) or  (II2) (where R^2 is trifluoromethyl, difluoromethyl, or methyl); **A** is hydrogen or methyl, and **B** is methyl or ethyl (with the exclusion of compounds in which A is methyl and B is ethyl), as well as specified intermediates thereof. E.g., column 4, lines 1-67. Among the disclosed compounds is a compound having the formula



(referred to in the Office Action at page 8 as Compound B). Applicants again point out that the benzene ring of the disclosed carboxanilide derivatives for which fungicidal activity is taught does not bear any ring substituent other than the amide and alkyl moieties shown in the above formula. In contrast, the benzene ring of Applicants' claimed compounds must bear a further fluorine substituent, a characteristic not found in the compounds disclosed in the reference. See Applicants' previous Amendment at page 9 and the current Office Action at pages 3-4. Applicants therefore submit that Yoshikawa et al would not alone suggest their claimed invention.

However, the Office Action at pages 8-9 relies on the Patani et al article to conclude that a hydrogen atom (such as on the benzene ring of Compound B of Yoshikawa et al) could be replaced with a fluorine atom (such as in Compound A of Applicants' invention) with the expectation that biological/pharmaceutical properties would not be altered. Applicants submit that the Patani et al article does not bridge the gap between Yoshikawa et al and their claimed invention. The Patani et al article beginning at page 3149 discusses several examples of bioisosterism relating to fluorine substitution, including some examples showing the interchangeability of hydrogen and fluorine (e.g., pages 3149-3150) and other examples showing the effect of replacing hydrogen with fluorine, hydroxyl, amino, or methyl groups (e.g., pages 3152-3155). However, the Patani et al article reveals that significant and unpredictable differences in biological activity can arise when making such changes. For example, **Figure 2 (Table 4)** shows an almost four-fold greater binding affinity

(as shown by a lower inhibitory concentration IC_{50}) when H is replaced by F in one naphthyl-fused diazepine but an almost twenty-fold greater binding affinity for a second naphthyl-fused diazepine. **Figure 3 (Table 5)** shows about 2.6 times greater anti-inflammatory activity for a difluoro androstane derivative compared to the mono-fluoro analog but only about 1.5 times greater anti-inflammatory activity for a related monofluoro androstane derivative compared to the dihydro analog having no fluoro substituent. Since both of the monofluoro compounds shown in Figure 3 have almost the same activity, one might expect that going from no fluorine to one fluorine and from one fluorine to two fluorines would result in a uniform increase in activity for each additional fluorine, but this was not the case. That is, in contrast to the dramatic increase in activity shown in Figure 2, only modest changes in activity are shown in Figure 3, but in each case the activities increase with fluorine substitution. **Figure 11 (Table 9)** bolsters Applicants' position. That is, in contrast to the increased biological activity found for the compounds shown in Figures 2 and 3, the fluorine-substituted test compound shown in Figure 11 (Table 9) exhibited about 1.6 times lower angio-tensin converting enzyme activity and about 2.4 times lower endopeptidase activity (as shown by greater inhibitory concentration IC_{50} in each test). In short, the data in Figure 2 (Table 4) and Figure 3 (Table 5) showed variably enhanced activity when F replaces H, whereas the data in Figure 11 (Table 9) showed reduced activity when F replaces H. That is, a proper reading of the Patani et al article shows that the specific degree of activity was both variable and unpredictable from compound to compound and from test to test. Therefore, even if one assumes that hydrogen can sometimes be replaced by fluorine or fluorine by hydrogen, that does not mean that one skilled in the art would be able to predict what activity or level of activity would result.

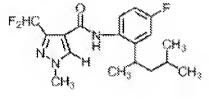
Examiner's response:

Although, as Applicant pointed out, it is not possible to predict the degree of change in activity when comparing compounds differing only by one Fluorine atom, the fact is that the prior art (Patani) teaches that by replacing an Hydrogen atom with a Fluorine, and particularly if the replacement occurs in an aromatic ring, the biological/pharmaceutical properties of the compound will be maintained within a certain

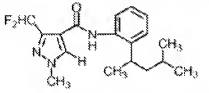
range of activity. The Fluorinated compound could be more or less effective (as pointed by Applicant when referring to Patani's examples), but it will likely still be active. Even in the most dramatic case pointed by Applicant (almost 20 fold increase in activity for the fluorinated compound shown in Table 4) the activity still remains at 1 micromolar for the Hydrogenated compound (compound 2a). So, the skilled in the art, knowing that a compound has a certain biological activity like compound B disclosed by Yoshikawa, will be motivated to replace any Hydrogen of the aromatic ring and expect the new fluorinated compound (compound A) to be also active with a reasonable expectation of success, since Patani teaches that compounds differing only by one or two fluorine atoms still maintain similar biological properties, even though the magnitude of the difference in activity cannot be predicted. There is nothing unexpected in observing even one order of magnitude increase or decrease in activity when replacing a Hydrogen atom with Fluorine.

Applicant argues that:

> In further support of their position, Applicants now present data in the form of Declarations under 37 C.F.R. 1.132 of Dr. Ulrike Wachendorff-Neumann and of Dr. Peter Dahmen showing unexpectedly enhanced biological activity of a fluorine-substituted compound of their invention disclosed in Example 14 of their specification and having the formula



compared with the corresponding unsubstituted comparison compound described in Example 3 of Yoshikawa et al and having the formula



In particular, in the *Leptosphaeria nodorum* test, Applicants' inventive compound exhibited an efficacy of 93%, whereas the comparison compound exhibited an efficacy of only 44%. Similarly in the *Sphaerotheca* test, Applicants' inventive compound exhibited an efficacy of 100%, whereas the comparison compound exhibited an efficacy of 78%. Although these compounds have a CHF_2 substituent on the pyrazole ring instead of a CF_3 group as found in Compounds A and B, Applicants submit that it is well established that even indirect comparisons, when "based on established scientific principles, can validly be applied to distinguish a claimed chemical process or product from that disclosed in the prior art." *In re Best, Bolton and Shaw*, 562 F.2d 1529, 195 U.S.P.Q. 430, 432 (C.C.P.A. 1977); see also *In re Blondel, Fouche, and Gueremy*, 499 F.2d 1311, 182 U.S.P.Q. 294 (C.C.P.A. 1974). Here, the only structural difference between the tested pair of compounds and the Compound A/Compound B pair is the presence of a CHF_2 group instead of a CF_3 group. Regardless of whether one might suppose that such a difference could conceivably have an effect on the results, Applicants have provided data in the specification showing that the inventive compound of Example 12 in which R^9 is CF_3 (i.e., Compound A) and the inventive compound of Example 14 in which R^9 is CHF_2 in fact exhibit almost identical activities in the tests reported in Table B (page 53), Table C (page 56), and Table D (pages 59 and 60, respectively). Applicants therefore submit that they have presented evidence showing that their invention is distinguishable from the cited references.

Applicants therefore respectfully submit that their claimed invention is not rendered obvious by Yoshikawa et al in view of the Patani et al article.

Examiner's response:

The above examples presented by Applicant confirm what was discussed in the previous segment, that replacing Hydrogen with Fluorine results in a fluorinated compound that retains the biological/pharmaceutical properties of the non-fluorinated compound within certain range. The order of magnitude in the different efficacies of the examples presented (2.1 fold greater for the fluorinated compound for the *Leptosphaeria nodorum* test and 1.3 fold greater for the fluorinated compound for the *Sphaerotheca* test) confirm the above assertions. Based on the magnitude of differences in efficacies observed in the prior art for fluorinated vs. non-fluorinated compounds (see Patani), the above differences (2.1 fold and 1.3 fold) presented by Applicant cannot be considered unexpected.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1628
July 3, 2011.